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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,090	03/11/2004	Ivan Richards	04-183 (400.147)	6030

65778 7590 12/18/2007

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
12/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,090	RICHARDS ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,16,17,19-21 and 30-47* is/are pending in the application.

4a) Of the above claim(s) *46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14,16,17,19-21 and 30-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/18/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/18/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant has added claims 32-47. Therefore, claims 1, 14, 16, 17, 19-21, and 30-47 are pending in the application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicants cannot file an RCE to obtain continued examination on the basis of claims that are independent and distinct from the claims previously claimed and examined as a matter of right (i.e., applicant cannot switch inventions). See 37 CFR 1.145. Any newly submitted claims that are directed to an invention that is independent and distinct from the invention previously claimed will be withdrawn from consideration and not entered. An RCE is not the filing of a new application (see MPEP 706.07(h)).

Newly submitted claims 46 and 47 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The invention of claims 1, 14, 16, 17, 19-21, and 30-45 (product claims) are related to the invention of claims 46 and 47 (process claims) as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the method of modulating the expression of a human CHRM3 gene in a cell can be practiced with another materially different product, for example a single stranded antisense oligonucleotide or a ribozyme. Since the inventions are distinct, to search for more than one of the inventions in the same application would not necessarily return art against the other invention and therefore presents an undue search and corresponding examination.

Since applicant has received an action on the merits for the originally presented invention (the product), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 46 and 47 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise

include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Applicant's amendments and/or arguments filed on 10/18/07, with respect to the Double Patenting rejection and the rejection under 35 U.S.C. 103(a) have been fully

considered and are persuasive. Therefore, these rejections have been withdrawn. However, upon further consideration, the rejections addressed below are newly applied.

Response to Priority

As explained in the office action mailed on 4/18/07, the effective filing date of instant claims 1, 14, 16, 17, 19-21, 30-38, 42 and 43 is determined to be that of PCT/US03/05028, which has an effective filing date of 2/20/2003.

It is noted that newly added claims 39-41, 44 and 45 are not supported by PCT/US03/05028 or any of the earlier priority documents, and therefore are accorded an effective filing date of 3/11/04, which is the filing date of the instant application.

PCT/US03/05028, nor any of the prior-filed applications, teach a limitation wherein in addition to the claimed percentages and types of modifications of claim 1, the molecule "further" includes the modifications recited in instant claims 39-41, thus altering the percentages of modifications within the molecule. Furthermore, neither PCT/US03/05028 nor any of the prior-filed applications teach a limitation wherein each strand has "no more than 3 consecutive ribonucleotides", as required by instant claims 44 and 45.

Applicant asserts that each of the instant claim limitations find support in application 60/363,124. Applicant points to passages from the '124 application as follows: pages 10-11 for a teaching that the nucleic acid molecule can have 1 to 10 phosphorothioate internucleotide linkages in both strands, one or more 2'-deoxy, 2'-O-

methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands; lines 6-11 of page 11 for a teaching that the nucleic acid molecule can, for example, have 1 to 10 phosphorothioate internucleotide linkages in either or both strands, 1 to 10 nucleotides of the sense and/or antisense strands being chemically modified to comprise 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. Importantly, none of these disclosures support the instant limitations of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, "or more" of each of the specific modifications; "one to ten or more" of each of the specific modifications; does not support the instant limitation of "further" including modifications in excess of the percentages recited in instant claim 1; and do not support the limitation "no more than 3 consecutive ribonucleotides".

Applicant asserts that because "the claimed molecules are 18 to 27 nucleotides in length, those skilled in the art can readily deduce that about 50 to 100 percent of the nucleotides in the antisense and sense strands may be chemically modified in accordance with the '124 application. Moreover, the '124 application provides numerous examples of chemically modified nucleic acid molecules having about 50 to 100 percent chemical modifications, especially at pages 55-57 of Table I, and in Figures 3-10. For instance, nucleic acid molecule 28254/28256 comprises about 50% chemical modifications on both strands. Other examples include, but are not limited to, 27653 and 27658 (both comprising 100% chemical modifications); 27655, 27654, 28254, 27662, 27659, 27660, 28244 (each comprising about 50 to 80 percent chemical modifications).

Accordingly, U.S. Provisional Application 60/363,124 provides ample support for the claim elements described above." Contrary to applicant's assertions, the examples disclosed in application '124 that fall within the instantly recited ranges are not sufficient to support the specific ranges that are being instantly recited. Applicant is relying upon specific examples of modified duplexes that fall within the instant ranges, although there is no disclosure in the '124 application to point one to a specific range of "about 50 to 100 percent" or "at least 50% of the nucleotides" of the nucleotides in the sense strand and antisense strand being chemically modified as instantly recited. Furthermore, the specific examples do not demonstrate the vast possibility of combinations of chemical modifications at the varying percentages as instantly recited.

Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation in each of the claimed priority documents.

Response to Claim Rejections - 35 USC § 103

Applicant's argument's that are relevant to the instant rejection of the claims under 35 U.S.C. 103(a) are addressed following the rejection below.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-41, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 39-41 are directed to the nucleic acid molecule of claim 1, wherein the molecule "further" includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of particular modifications. However, the instant specification does not teach a limitation of further comprising modifications in addition to the percentages and configurations of modifications recited in claim 1.

Claim 44, and by dependency claim 45, are directed to a chemically modified nucleic acid molecule wherein each strand "has no more than 3 consecutive ribonucleotides", which is a limitation that is not disclosed in the instant specification.

Therefore, the effective filing date of claims 39-41, 44 and 45 is considered, for purposes of prior art, to be 3/11/04, which is the filing date of the instant application.

A review of the specification does not reveal support for where the various claim amendments are found and therefore they constitute new matter. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation discussed above.

Claims 1, 14, 16, 17, 19-21, and 30-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is directed to a chemically modified nucleic acid molecule, wherein about 50 to 100% of the nucleotide positions of each strand comprise chemically modified nucleotides independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-flouro, 2'-deoxy, phosphorothioate and abasic moieties and one or more of the purine nucleotides are 2'-O-methyl and one or more of the pyrimidines are 2'-deoxy-2'-fluoro. The claims are further directed to the incorporation of specific types of chemical modifications at varying numbers of positions.

Although the specification discloses examples of nucleic acid sequences with chemical modifications (tables and figures), the specification does not describe a sufficient number of nucleic acid that are chemically modified at about 50 to 100% of the nucleotides of each strand with the instantly recited modifications or combinations of modifications that result in active molecules to describe the instant genus, which encompasses a huge number of possible configurations. The scope of the claims is so broad that one of ordinary skill in the art would not be able to envisage the genus of claimed nucleic acid molecules that retain activity such that the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing.

The skilled artisan would not be able to envision which nucleic acid molecules would result in active molecules without undue experimentation and therefore would not be able to recognize that applicant was in possession of the instant genus of molecules that retain activity. Applicant is not claiming any double stranded nucleic acid molecule directed to a CHRM3 RNA sequence comprising SEQ ID NO: 305, but is rather claiming the subset of molecules that are extensively modified with the instant modifications. The ability for a specific nucleic acid to direct cleavage of a target RNA via RNAi must be experimentally determined and cannot be predicted. The extensive chemical modification that is instantly recited introduces an extra level of uncertainty. Since applicant has not provided any data representing the activity of the instant genus of molecules, one of skill would not be able to envision which molecules would result in active molecules in order to be able to recognize that applicant was in possession of the instant genus of molecules at the time of filing.

Although applicant has described some nucleic acid molecules with varying levels of varying types of chemical modifications, applicant has not described a sufficient number of nucleic acid molecules that are chemically modified at about 50 to 100% of each strand with a sufficient number of combinations of modifications within the instant genus to describe the breadth of the instant genus and furthermore applicant has not described a single nucleic acid molecule that is 100% chemically modified with the instant configuration of modifications that retains activity.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)

The instant claims are directed to nucleic acid molecules comprising a huge genus of chemical modifications and/or possible combinations of chemical modifications at varying percentages. The instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the claimed invention because the specification does not provide a description of a sufficient number of species of nucleic acid molecules with a sufficient number of species of chemical modifications that result in active molecules to adequately describe the instant genus.

As supported by the teachings of Elbashir et al. regarding dsRNA molecules that are 100% modified with 2'-O-methyl or 2'-deoxy modifications, as discussed in the instant rejection under 35 USC 103, there is no known or disclosed correlation between the structure instantly claimed and a given function to show that the applicant was in possession of the claimed genus at the time of filing.

Applicants have not described a structure to define the instantly recited molecules that have modifications at about 50 to 100% of the nucleotides of each strand that result activity, the desired activity of mediating RNAi, the activity as explained in the instant specification. Additionally, applicants are broadly claiming various combinations of chemical modifications, although applicant has not demonstrated that these molecules would be active and certain modifications within the instantly claimed genus have been shown to totally inactivate RNAi. Elbashir et al. teach that 100% modification of one or both strands of a siRNA with 2'-deoxy or 2'-O-methyl modifications abolished RNA interference (see page 6882). Applicant has not described a structure that would lead one of ordinary skill to construct only those that result in active molecules.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 14, 16, 17, 19-21, and 30-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001) (of record and cited on the PTO-892 mailed on 7/24/06), in view Nyce (WO 99/13886) (of record and cited on the PTO-892 mailed on 7/24/06), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000) (of record and cited on the PTO-892 mailed on 7/24/06), Matulic-Adamic et al. (US 5,998,203), Kurreck et al. (Nucleic Acids Research, 2002, Vol. 30, No. 9, pages 1911-1918), Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

The instant invention is directed to a chemically modified nucleic acid molecule comprising a sense and an antisense strand, wherein each strand is 18 to 27 nucleotides in length specific for a CHRM3 RNA sequence comprising SEQ ID NO: 305, wherein about 50 to 100% of the nucleotide positions of each strand comprise chemically modified nucleotides independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-flouro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and one or more of the purine nucleotides are 2'-O-methyl and one or more of the pyrimidines are 2'-deoxy-2'-fluoro. The claims are further directed to various quantities/configurations of the chemical modifications, terminal caps, overhangs, and a composition comprising the molecule and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. teach siRNAs comprising a sense and a separate antisense strand, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. The siRNAs taught by Elbashir et al. mediated RNAi via RISC. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications that retained activity, which meets the instant limitation of "about 50" percent. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs were the most efficient triggers of RNAi (see abstract). Elbashir et al. teaches chemical modification of the 3' overhangs. Furthermore, the instant specification does not define "terminal cap" and it is not a term of the art. Therefore, the terminally modified siRNA molecules of Elbashir et al. meet the instant limitation of comprising a terminal cap. Furthermore, Elbashir et al. teach the presence of a 5'-terminal phosphate group on the antisense strand (see page 6886, column 2).

It is noted that Elbashir et al. teaches that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, none of the instantly recited claims are limited to this scope.

Elbashir et al. do not teach double stranded nucleic acid molecules specific for CHRM3 RNA. Elbashir et al. do not teach modifications other than 2'-O-methyl or 2'-deoxy, do not teach abasic moieties, and do not teach a composition comprising the molecule and a pharmaceutically acceptable carrier or diluent.

Nyce teaches antisense oligonucleotides that attenuate the expression of target mRNA. The oligonucleotides are preferably up to about 30 nucleotides in length, more preferably up to about 21 nucleotides in length (see page 16). Nyce teaches antisense oligonucleotides targeted specifically to human muscarinic acetylcholine receptor 3 (CHRM3) (see page 54). Nyce teaches phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73) for enhancing the uptake of the oligonucleotides. The 100% substituted oligonucleotide comprises a phosphorothioate at the 3' end. Nyce teaches compositions comprising the oligonucleotide and a pharmaceutically acceptable carrier (see page 77). Nyce teaches surfactants or surfactant components bound to the 5' and/or 3' ends or the oligonucleotides for enhancing uptake of the oligonucleotide (see page 80), meeting the instant limitation of "terminal cap".

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at

the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications that resulted in interference activity.

Kurreck et al. teach optimization of antisense oligonucleotides containing LNAs (see abstract). Kurreck et al. teach that LNAs have a high affinity for the complementary target RNA and have high stability. Kurreck et al. each that LNAs have high *in vivo* efficacy in the absence of any toxicity and that further experiments to stabilize aptamers, ribozymes and DNA enzymes with LNA are in progress (see page 1917, second column).

Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs. Bertrand et al. teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Bertrand et al. teach that siRNA activity, but no antisense oligonucleotide activity, was observed in mice, probably due to

the lower resistance to nuclease degradation of antisense oligonucleotides (see abstract). Bertrand et al. teach that siRNAs are composed of small double-stranded RNA oligonucleotides with a length of 21/22 bases (see page 1000, column 1). Bertrand et al. teach that delivery is a very similar issue for both approaches and that siRNAs are very promising tools for gene inhibition *in vivo* (see page 1000, column 2).

Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity (see page 4503). Braasch et al. teach goals for improving oligonucleotides including: improve pharmacokinetics, tissue distribution, and targeting; characterize the mechanism of RNA interference and its full potential for inhibition of gene expression for cell culture studies; use RNAi for *in vivo* inhibition of mammalian gene expression; perform comparative studies to demonstrate the relative strengths of different oligomer chemistries for given applications (i.e. morpholino versus RNAi) (see Table 2). Braasch et al. teach that if good *in vivo* uptake can be achieved, RNAi might significantly improve the ability of oligonucleotides to have an impact (see page 4509).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity and teach compositions comprising the oligonucleotides with a pharmaceutical carrier. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate

backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to synthesize a double stranded nucleic acid molecule with the structural characteristics (size, overhang, and types of chemical modifications) taught by Elbashir et al., that is targeted to CHRM3 RNA, wherein **about** 50 to 100% of the nucleotides of each strand are modified with each of the instant types of chemical modifications or combinations of chemical modifications, and wherein the double stranded nucleic acid molecule is in a composition with a pharmaceutically acceptable carrier or diluent.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al., wherein the nucleic acid is specific for CHRM3 RNA comprising instant SEQ ID NO: 305 because Nyce teaches antisense oligonucleotides targeted specifically to human muscarinic acetylcholine receptor 3 (see page 54) in pharmaceutically acceptable carriers and teaches extensive chemical modification of antisense oligonucleotides.

Since Nyce et al. teaches antisense oligonucleotides specific for CHRM3 in pharmaceutically acceptable carriers and teaches chemical modifications, one would have been motivated to utilize another inhibitory molecule that acts via a sequence

specific mechanism, such as an siRNA, instead of the antisense oligonucleotide, as siRNAs were known to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides and were known to have increased resistance to nuclease degradation when compared to antisense oligonucleotides *in vivo*, as evidenced by Bertrand et al.

Furthermore, one would have been motivated to incorporate the phosphorothioate, 2'-deoxy and 2'-O-methyl modifications of the oligonucleotides of Nyce, as well as the pharmaceutically acceptable carrier of Nyce into the siRNA, as each of these were known to enhance the uptake of the oligonucleotides. The siRNA molecules of Elbashir et al. comprise known chemical modifications. Therefore, one would have certainly been motivated to incorporate other types and configurations of chemical modifications that were known in the art to enhance the activity of nucleic acid therapeutics into the siRNA duplexes of Elbashir et al. in order to optimize the activity of the molecules.

Similarly, one would have been motivated to incorporate 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. or Matulic-Adamic et al., as well as 2'-O methyl or 2'-deoxy modifications, as taught by Elbashir et al. and Matulic-Adamic et al., as well as abasic moieties and phosphorothioates, as taught by Matulic-Adamic et al., and LNAs as taught by Kurreck et al., as each of these chemical modifications, as well as various combinations of chemical modifications, were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids, as taught by Matulic-Adamic et al. and Kurreck et al.

The instant genus is huge, encompassing nucleic acid molecules that are modified at about 50 to 100% of the positions of each strand with a multitude of chemical modifications or combinations of chemical modifications that were known in the nucleic acid therapeutics art, such as the antisense and ribozyme art. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules at varying percentages. Due to the breadth of the instant claims, the teachings of Elbashir et al. are considered to be motivation with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the huge genus of molecules that are being instantly claimed, the teachings of Elbashir et al. are considered to offer motivation to test various types of known chemical modifications at different percentages in order to optimize the activity of the molecule.

It is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 100).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Therefore, one would have been motivated to incorporate chemical modifications at about 50 to 100% of the nucleotide positions of each strand because Elbashir et al. teach successful inhibition of "about 50" percent of the nucleotides (8/42) and teach testing two types of chemical modifications extensively in siRNA molecules, and Parrish et al. and Matulic-Adamic et al. each teach extensive chemical modification of nucleic acids with successful inhibition of target gene expression, the inhibition of Parrish et al. occurring via RNA interference.

Furthermore, Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity. Braasch et al. further recognize that goals to improve RNAi can be accomplished by utilizing chemical modifications. Since Braasch et al. teach that chemical modifications yield more potent and more selective antisense oligomers, such as oligomers for RNAi, and Elbashir et al., Nyce, Matulic-Adamic et al., and Parrish et al. teach modified nucleic acid molecules that inhibit target gene expression, the gene expression of Elbashir et al. and Parrish et al. being inhibited by RNAi, one would have been motivated to synthesize duplexes with different levels of known modifications to optimize the activity of the molecule. Furthermore, Elbashir et al. teaches testing siRNA molecules with different levels of 2'-deoxy modifications and therefore the number of ribonucleotides in the double stranded molecule is also considered within the realm of routine optimization.

Kurreck et al. teaches the benefits of incorporating LNAs into antisense oligonucleotides and offers motivation to test these modifications in order to stabilize other inhibitory molecules by teaching "Further experiments to stabilize aptamers, ribozymes and DNA enzymes with LNA are in progress "(see page 1917, second column). Therefore, Kurreck et al. supports the position that it would have been obvious to incorporate chemical modifications that are known in the art to benefit one type of nucleic acid inhibitory molecule into other nucleic acid inhibitory molecules that also desire increased stability in order to routinely optimize the molecule.

With regards to the specific configurations and percentages of known chemical modifications, it would have been prima facie obvious to perform routine optimization to determine optimal double stranded nucleic acid molecules, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular range used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology, as evidenced by Braasch et al.

For example, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise

experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity and to deliver nucleic acids in a composition with a carrier.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Olie et al. and Braasch et al., into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Nyce, Kurreck et al., Matulic-Adamic et al., Parrish et al., Braasch et al. and Olie et al., wherein each of the molecules face the same challenges, and each of which can be improved with modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for different combinations of modifications that are known to benefit oligonucleotides at various percentages to benefit the double stranded nucleic acid molecules of Elbashir et al. targeted to human CHRM3 RNA, as evidenced by the modified antisense oligonucleotides that are specific for CHRM3, as taught by Nyce.

Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive

modification of double stranded nucleic acid molecules and Olie et al. teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir et al. is considered obvious to try and within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments pertinent to the instant rejection under 35 USC § 103

Applicant argues that applying the framework of the KSR decision, the Federal Circuit held it necessary to demonstrate that the prior art provides reasons to make the particular invention and not merely general guidance. Applicant points to *Pharmastem*

Therapeutics v. Viacell to support this argument. Importantly, in the instant case the examiner is not relying on mere general guidance in the prior art. The prior art provides reasons to make chemically modified siRNA molecules, as explained in detail in the rejection under 35 U.S.C. 103(a), above. It was known that siRNA molecules face delivery challenges, challenges of which were known to be decreased by incorporating known chemical modifications. Contrary to *Pharmastem Therapeutics v. Viacell*, the prior art in the instant case teaches each of the instantly recited chemical modifications, teaches the benefits of incorporating them, and exemplifies that it is routine in the field to test them at various percentages and in various configurations.

Applicant points to *Takeda Chemical Industries v. Alpharma* to illustrate the importance of having a finite number of identified, predictable solutions for a finding of obvious. Importantly, each of the instantly recited chemical modifications were known to enhance the activity of various types of nucleic acid inhibitory molecules in the field. Although there may not be 100% predictability of the outcome of every possible combination of the instantly recited modifications, there is certainly a level of predictability that the modifications will enhance the activity of the molecule and determining the optimal combinations and percentages is within the realm of routine optimization. *Takeda Chemical Industries v. Alpharma* refers to actual chemical changes to a known compound, which is not the same as incorporating different combinations or percentages of known chemical modifications that are known to benefit nucleic acid inhibitory molecules including siRNAs. Applicant has not altered the known

chemical modifications in any way, but is rather claiming a huge genus of possible combinations of them.

Applicant argues that the cited references, alone or in combination, fail to provide a reason or motivation to modify the double stranded molecules in the specific pattern and to the specific extent as claimed. Applicant asserts that the cited references do not teach those skilled in the art how to predict which of the potentially millions of modified molecules might be efficacious. Importantly, applicant is not claiming a specific modification that they have demonstrated some unexpected property that has resulted therein, but is rather broadly claiming a huge genus of double stranded nucleic acid molecules that have a vast possibility of combinations of chemical modifications at varying percentages and is asserting that this genus would give results other than expected in the art. As explained in the rejection under 35 U.S.C. 112, 1st paragraph (written description) above, applicant has not demonstrated any structural characteristic to define which molecules within the instantly claimed huge genus would have resultant activity. The rejection under 35 U.S.C. 103(a) is based on the previous knowledge in the art regarding the benefits of each of the specific modifications that are instantly claimed, as well as the benefits of incorporating modifications at varying percentages. The prior art strongly suggests that it would be obvious to try the known chemical modifications in varying configurations and percentages and teaches the benefits of each of the specific modifications that are being instantly claimed. This situation is not identical to the situations pointed to by applicant in the case law.

Applicant argues that at the time of the present invention, there was no reason for a skilled artisan to apply the chemical modifications of single stranded antisense oligonucleotides to double stranded RNA molecules. Although it was believed that double stranded RNA molecules were more stable than single stranded antisense oligonucleotides, it was still known in the art that both single and double stranded oligonucleotides faced similar delivery challenges, each which could be aided with chemical modifications, as evidenced by the teachings of Braasch et al., as explained above.

Furthermore, Elbashir et al. and Parrish et al. teach the incorporation of chemical modifications that were known to benefit antisense oligonucleotides into a double stranded molecule that act via interference, further evidencing that it was known in the art to test such modifications for RNAi activity. Furthermore, Bertrand et al. specifically teaches that delivery is a very similar issue for both approaches, antisense oligonucleotides and double stranded duplexes. Therefore, the prior art teaches reasons to enhance the activity of the double stranded molecules with chemical modifications that were known in the art to be incorporated for this exact reason.

Applicant argues that Nyce merely suggests CHRM3 is a potential target based on antisense oligonucleotide studies and does not mention modified double stranded molecules. It is agreed that Nyce teaches CHRM3 as a target for antisense oligonucleotide inhibition, which offers motivation to target and inhibit CHRM3 in a sequence specific manner. Furthermore, the oligonucleotides of Nyce comprise chemical modifications to enhance the activity of the oligonucleotides. Applicant argues

that there is not an expectation of success based merely on the fact that a gene is known to be associated with a certain ailment. Contrary to applicant's argument, there is certainly a reasonable expectation of success in targeting and inhibiting a particular gene with siRNA molecules that has already been studied and inhibited with antisense oligonucleotides. Furthermore, there is motivation to inhibit a gene that is known to be associated or overexpressed with respect to a disease with an antisense oligonucleotide or a siRNA if the sequence is known in the art because these molecules are known to be beneficial inhibitory agents that act via a sequence specific mechanism.

Applicant points to *Cardiac Pacemakers, Inc. v. St. Jude Medical*, for a statement that recognition of a need does not render obvious the achievement that meets the need. However, in the instant case, the examiner is not relying upon recognition of a need to establish reasonable expectation of success, but is rather relying upon recognition of a need and the fact that the target is known in the art to be a target for antisense oligonucleotide inhibition. The fact that this target was known to be a target for antisense oligonucleotides renders it obvious to target the same sequence with another inhibitor that is known in the art to be preferred to antisense oligonucleotides, such as siRNAs, as evidenced by Bertrand et al. Applicant is not claiming any therapeutic effect. The association of CHRM3 with any disease state would offer a reason to target the gene, wherein in the instant case there is strong motivation to utilize a sequence specific inhibitor, in view of the teachings of Nyce.

Applicant points to *In re Gordon* for a statement that the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability. Again, applicant is not claiming a specific modification but is claiming a huge genus of modifications/combinations of modifications at varying percentages that applicant has not exemplified to be successful. In view of the references relied upon by the examiner, there was certainly a suggestion in the prior art regarding the desirability to incorporate known chemical modifications into siRNA molecules to enhance the activity of the molecules, the same reasons of which the same modifications were utilized with other sequence specific inhibitory molecules, such as antisense oligonucleotides or ribozymes.

Applicant argues that Parrish does not teach CHRM3 or suggest the instant size range for chemically modified dsRNA molecules. It is noted that the instant rejection is a rejection under 35 U.S.C. 103, rather than 35 U.S.C. 102 and therefore it is the combination of references that is relied upon by the examiner. Parrish was not relied upon for such teachings and therefore such arguments are not relevant. Parrish teaches siRNA molecules within the instant size range, demonstrating that the size is not novel for a siRNA and Parrish teaches extensive chemical modification of long dsRNA with 2'-deoxy-2'-fluoro modifications, a modification recited in the instant claims, wherein the extensively modified long dsRNA resulted in interference activity. Applicant argues that Parrish does not teach any of the instantly recited modifications. Contrary to applicant's argument, Parrish teaches 2'-deoxy-2'-fluoro modifications and is relied upon for demonstrating that is was known to incorporate such modifications into dsRNA

molecules that result in interference activity, importantly when the molecules are extensively modified. Furthermore, applicant asserts that Parrish expressly describes that 2'-deoxy modification of cytidine is not tolerated and points to a passage in Parrish that teaches that such modification substantially decreased interference activity. It is noted that a substantial decrease in activity is not equivalent to the modification not being tolerated, as asserted by applicant. Furthermore, applicant is not claiming any specific configuration that is identical to the teachings of Parrish. Parrish teaches successful interference activity with extensive modification of long dsRNA molecules with 2'-deoxy-fluoro modifications in uridines. Contrary to applicant's assertion, those skilled in the art would not completely avoid 2'-deoxy-2'-fluoro cytidine modifications based on the teaching so Parrish et al. that extensive modification resulted in a decrease in activity. Furthermore, Parrish et al. does not teach that cytidines should not be subject to 2'-deoxy modification if interference activity is desired, as explained above. Applicant is leaping from the instant claims that require 1 or more 2'-deoxy-2'-fluoro modification to the decrease in activity in cytidines when a long dsRNA is extensively modified with such modifications, when the instant claims are not even limited to cytidine modification. Furthermore, the instant claims directed to 2'-deoxy-2'-fluoro pyrimidine modifications include the modifications of Parrish of uridine, which resulted in successful interference activity. Furthermore, applicant asserts that Parrish does not teach such modifications simultaneously in both strands. Parrish was not relied upon for such a teaching and is not required to teach modification of both strands

to offer motivation to routinely optimize dsRNA molecules by testing modifications that resulted in successful interference activity.

Applicant argues that the teachings of Elbashir et al. suggested to the skilled artisan to design siRNAs without any modifications other than 2'-deoxythymidines at the 3'-end. Applicant's conclusions regarding the Elbashir et al. reference are considered erroneous. Elbashir et al. teaches successfully modifying siRNA duplexes at 8/42 positions with 2'-deoxy modifications and teaches that 100% modification abolished activity. Not one of the instantly pending claims are directed to the scope of 100% modification with 2'-deoxy or 2'-O-methyl modifications, the only scope that Elbashir et al. could possibly be construed as teaching away from. Elbashir is silent as to any results in between the 8/42 positions being successfully modified and the 100% modification abolishing activity. Elbashir et al. offers motivation to test chemical modifications and certainly did not lead those skilled in the art away from modifying siRNA molecules. Elbashir et al. teaches that duplexes with 3' overhangs are the most efficient triggers of degradation. Simply because the teachings of Elbashir et al. regarding the presence of modified overhangs offered motivation in the art to incorporate overhangs and to modify them does not mean that Elbashir et al. teaches away from optimizing the remainder of the molecule via incorporating other known chemical modifications at varying percentages that Elbashir et al. is completely silent to. Applicant is drawing conclusions from the Elbashir et al. reference that Elbashir et al. is silent to.

Applicant points to a passage from Elbashir et al., "2'-deoxy substitution of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-0-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." Applicant concludes that the statement "more extensive" could have only been intended to modify 2'-deoxy and not 2'-O-methyl as the first sentence refers to 2'-deoxy substitutions. Contrary to applicant's dissection of the Elbashir et al. passage, the "More extensive" phrase is being extracted out of the sentence by applicant. The sentence reads "More extensive 2'-deoxy or 2'-O-methyl modifications..." and is interpreted as referring to the 100% modification that is taught by Elbashir et al. to abolish activity. The only "more extensive" modification that is taught by Elbashir is the 100% modification, as Elbashir et al. only teaches the successful 8/42 modification and the unsuccessful 100% modification.

Applicant asserts that since Elbashir et al. teaches successful results at one percentage and unsuccessful results at another percentage, one could not predict what specific position levels or types of chemical modifications amongst hundreds of thousands or more of potential modification patterns would lead to a "successful" RNA duplex. It is agreed that the Elbashir et al. reference alone would not lead one to predict the specific combinations and percentages of known modifications that would necessarily work. It is the state of the prior art as a whole that suggests that each of the instantly recited chemical modifications yield beneficial properties to delivering nucleic

acid therapeutics and it would be obvious to try each of the instant modifications in different combinations and percentages to routinely optimize the molecules. The pending rejection is a rejection under 35 U.S.C. 103 rather than 102 because it is the combination of references that renders the instant claims obvious. Applicant is claiming a subset of chemical modifications, wherein each modification was known in the art to benefit nucleic acid inhibitory molecules. Although applicant is claiming the modifications in a way that the claims embrace a large genus of possible chemical medications, applicant has not demonstrated that this genus of molecules yield any unexpected property. The state of the art is such that it was known to routinely optimize antisense oligonucleotides, ribozymes, and siRNA molecules via incorporating the instantly recited chemical modifications.

Combining the instant modifications, each of which were known in the prior art, was certainly within the grasp of a person of ordinary skill. As explained above, applicant has not demonstrated any unexpected property of the instantly recited percentages/configurations of known chemical modifications. Furthermore, consistent with KSR, there was a design need to solve a problem, the problem of delivery of siRNA molecules. It was known that the known chemical modifications enhance delivery of nucleic acid therapeutics. Therefore, a person of ordinary skill had good reason to routinely optimize the molecules via combining the modifications at varying percentages within the broad scope of the instant claims. The instant claims are considered to be a combination of prior art elements according to known methods to yield predictable results. Although the results may not be 100% predictable, as there are embodiments

that may not be successful, there is a level of predictability of combining the prior art elements that are taught to benefit delivery. It would be obvious to try different combinations and percentages, as determining the best combinations and percentages is within the realm of routine optimization.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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